REMARKS

Amendments in the claims

Following entry of the present amendment, Claims 12–32 are pending in the present application of which Claims 20–28 are presently withdrawn from consideration. Claims 1–11 were previously canceled.

Claim 12 is corrected to recite a matrix free of solubilizers. Support for such is found in originally filed Claim 1 (prior to translation) and p. 1, line 3, p. 5, line 22, p. 6, line 18, and p. 10, line 24. *See infra,* Amended English Translation of Application.

Claims 12 and 13 are amended to recite that the matrix is storage-stable for at least 6 months. Support for such is found in the specification as filed at least at p. 3, lines 3-5.

Claim 16 is amended herein to further enhance clarity by replacing "0" with "zero".

New Claim 32 recites a matrix free of polyvinyl pyrrolidone. Support for such new claim is found in the specification as filed, at p. 2, lines 19-23 and Example 2b.

No new matter is introduced as a result of the present amendment and no change in inventorship has resulted from the proposed amendment.

Amendments in the drawings

Applicant submits one replacement sheet herewith to amend the description of Figure 1. The replacement Figure 1 contains identical subject-matter as Figure 1 submitted with the present application as filed except to clarify the description of the figure. Specifically, replacement Figure 1 states, with the more appropriate translation, that the matrix in Figure 1 is one "with rotigotine particles after dispersion without solubilizers and/or emulsifier.

No new matter is introduced as a result of the present amendment.

AMENDED ENGLISH TRANSLATION OF APPLICATION

Applicant originally filed this national phase application off of a PCT Application (PCT/EP2003/014902), which was originally filed in the German language. In translating PCT/EP2003/014902 into the English language, the German words "löslichkeitsvermittlern" and "lösungsvermittlers" were translated to solvent or solvents. *See* p. 1, line 3, p. 5, line 13, p. 5, line 22, p. 6, line 18, p. 10, line 24, p. 18, line 5, and Figure 1. As set forth in the 37 CFR § 1.132 declaration of Keith Ormand (attached to the current response), the more appropriate translation of the German words "löslichkeitsvermittlern" and

"lösungsvermittlers" is solubilizer or solubilizers. Accordingly, at p. 1, line 3, p. 5, line 13, p. 5, line 22, p. 6, line 18, p. 10, line 24, p. 18, line 5, and Figure 1, the more appropriate English word for "löslichkeitsvermittlern" and "lösungsvermittlers" is solubilizer or solubilizers.

RESPONSE TO OFFICE ACTION DATED 24 NOVEMBER 2009

Substance of the 27 April 2010 Interview

Applicant appreciates the courtesy shown by Examiner Welter and her supervisory examiner, Examiner Landau, in granting a telephone conference with Harness Dickey attorneys Leanne Rakers and Molly Edwards on 27 April 2010. Applicant also notes receipt of the Interview Summary dated 30 April 2010. The Interview Summary states that "Applicant noted that the current translation of the instant specification is incorrect and should state 'free of solubilizers' rather than 'free of solvents'." However, in the telephone conference, the parties discussed fixing a translation issue of the specification. Specifically, Applicant explained that the more appropriate translation of the German words "löslichkeitsvermittlern" and "lösungsvermittlers" is solubilizer or solubilizers. The Examiner suggested filing a 37 CFR § 1.132 Declaration indicating the more appropriate translation. *See* the 37 CFR § 1.132 Declaration of Keith Ormand (attached to the current response).

Examiner Landau also questioned in the telephone conference whether the specification provides any examples of a matrix with amorphous particles of a maximum mean diameter of 30 μm. Applicant explained that the specification is replete with examples of Applicant's invention. Applicant sets forth the answer to Examiner Landau's question more fully below. *See e.g. infra,* Section 2.

No agreements were made regarding patentability of the pending claims. Although, this paper takes into account the discussions during the telephone conference on 27 April 2010.

Rejection under 35 U.S.C. §103(a)

Claims 12–19 and 29-31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,906,830 ("Farinas") in view of EP 1256340 ("Lauterbach"). This rejection is respectfully traversed.

1. No Guidance to Select Rotigotine From Six Broad Drug Categories

As admitted by the Examiner on p. 4 of the Office Action, Farinas does "not explicitly teach a transdermal drug delivery system comprising a rotigotine base." Farinas instead mentions at least six large broad categories:

> Any number of drugs can be incorporated into transdermal delivery systems using the present methodology, so long as they are suitable for transdermal or transmucosal administration and give rise to the desired effect....Drugs which may be incorporated into transdermal systems using the present technique include, but are not limited to: analgesic serotonergic agonists; narcotic agonists and antagonists; anthistamines; antiinflammatory agents including NSAIDS (nonsteroidal antiinflammatory agents), benzodiazepines, dopaminergic agonists and antagonists; hormones, particularly steroids, and hormone antagonists; and antipsychotic agents.....

See Farinas, at col. 7. However, at p. 9 (emphasis added) the Examiner still "contends that it would have been obvious to an artisan of ordinary skill at the time the invention was made to select from the **finite** possibilities of drugs and excipients mentioned in Farinas to arrive at the instantly claimed invention." The amount of drugs which would fall under these six broad categories of drugs in Farinas is endless, and thus, there are well over a finite number of possibilities.

However, even in there was some pattern of preference for selection of dopaminergic agonists and antagonists (which is not admitted herein) from Farinas, the Examiner assumes that all dopaminergic agonists and antagonists are effective in a matrix, much less Applicant's and/or Farinas' matrix. An ordinary skilled artisan reading Farinas would have had to first pick a compound considered to act on at least one dopamine receptor, then select an agonist, test the dopamine agonists, select 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthol, and then rotigotine. This selection process, without any guidance from Farinas, may involve:

(1) Review of approximately 169 compounds that can act on dopamine receptors;

(2) Narrowing to approximately 57 compounds that are dopamine agonists;

(3) Testing at least the 57 agonists or partial agonist compounds;

(4) Choosing 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol; and

(5) Finally, selecting rotigotine.

Clearly, such a multi-step selection can only be made in hindsight with guidance from Applicant's specification to arrive at the claimed invention. At best, the very large number of possible compounds provides an invitation to "try" or "experiment" on the large number of dopamine agonists, which would include rotigotine. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d at 1359, emphasis added.

Furthermore, even if you were to try each of the large number of possible choices in the hope of eventually arriving at a successful result, Farinas reports "heating a particular polymer-admixture" at col. 6. The Examiner asserts at p. 9 of the Office Action that there is "no objective evidence" that "rotigotine base is sensitive to oxidation." Despite sensitivity to oxidation being evident from the structure of rotigotine itself, Applicant directs the Examiner's attention to the European Public Access Report which states "[s]ince rotigotine is sensitive to oxidation, 3 antioxidants have been added to the matrix so as to prevent oxidative degradation: sodium metabisulfite, α-tocopherol and ascorbyl palmitate." *See* http://www.ema.europa.eu/humandocs/PDFs/EPAR/neupro/062606en6.pdfm (2006), submitted herewith.

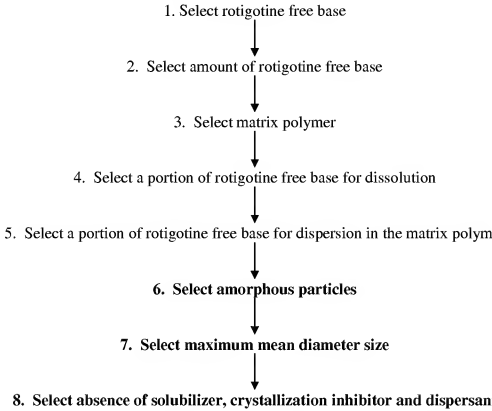
With no guidance for the selection of rotigotine and given Farinas' report on heating, such invitation to "try" or "experiment" on such a large number of compounds is not enough to establish a presumption of *prima facie* obviousness. Furthermore, the secondary reference, Lauterbach, also does not provide any motivation to utilize rotigotine in Farinas' matrix.

2. No Guidance to Construct Applicant's Matrix

Not only is there no motivation for one of ordinary skill in the art to select rotigotine for inclusion in the matrix of Farinas, even after selecting rotigotine, there is no guidance in Farinas, Lauterbach, or the alleged combination, to make the multiple selections one of

ordinary skill in the art would have to make to construct Applicant's matrix using rotigotine. The Examiner failed to address this flow chart set forth in Applicant's RCE dated 6 March 2009, and thus, Applicant provides it again.

After reviewing the cited art, to construct the matrix of Claim 12, for example, one of ordinary skill in the art would have to:



Again, at best, the eight selections plus the infinite number of sub-selections, one of ordinary skill in the art would have to make by reading Farinas in view of Lauterbach without any guidance, provides only a possible invitation to "try" or "experiment".

2.1. No Guidance Toward the Selection of a Maximum Mean Diameter Size of the Amorphous Particles

With respect to selection #6 and #7 above, Applicant notes in the specification as filed that

> [u]pon observation through the microscope, it turned out that the amorphous rotigotine particles are surprisingly finely distributed in the silicon matrix, with a maximum size of roughly 30-40 µm, but mostly smaller than 20

> μm (FIG. 2). Even after six months storage at room temperature, the amorphous rotigotine particles in the silicon matrix showed no tendency to recrystallize.

See specification as filed, at p. 5, lines 1-5. An exemplar microscopic photograph of the amorphous particles with a maximum mean diameter of 30 μm is shown in Figure 2 of Applicant's specification as filed. Furthermore, the production or formulation of the system in Figure 2 with amorphous partical size having a maximum mean diameter of 30 μm is described in Example 1 of the specification as filed.

The Office Action states "since Farinas et al appear to have the same method of making the transdermal patch as the instant invention, it is the position of the Examiner that rotigotine base as amorphous particles with a maximum mean diameter of 30 μm in the drug reservoir layer would be an obvious expected property of the transdermal delivery system of Farinas et al as in *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)." *In re Spada* held that "it was reasonable for the PTO to infer that the polymerization by both Smith and Spada of identical monomers, employing the same or similar polymerization techniques, would produce polymers having identical compositions." *Id.,* emphasis added.

However, it is well known that particle size depends on, amongst other factors, (1) the drug employed, (2) the formulation employed and (3) the manufacturing process. Farinas does not recite rotigotine or rotigotine base and does not disclose, teach, or suggest a matrix free of a solubilizer, crystallization inhibitor and dispersant. Contrary to *In re Spada,* Farinas fails to disclose the same drug as Applicant *(i.e.* rotigotine) or the same technique. Thus, it can not be obvious from Farinas what particle size would result from rotigotine free base employed in Applicant's claimed matrix. Farinas, Lauterbach, or any alleged combination of such, thus, fail to render obvious, or provide any guidance toward the selection of, a maximum mean diameter size of the amorphous particles.

2.2. No Guidance Toward the Selection of a Matrix Absent Solubilizer, Crystallization Inhibitor and Dispersant

With respect to selection #8 above, as recognized by the Examiner (Office Action bridging p. 7-8), "Farinas still teaches that crystallization inhibitors may be incorporated in its transdermal delivery systems." Farinas also discloses that, among other things, crystallization inhibitors "or other types of additives [are] useful for facilitating transdermal

drug delivery." *See* Farinas, col. 5, lines 47-49. Lauterbach and WO 99/49852 teach use of additives to improve the solubility of rotigotine in a matrix. Specifically, as discussed in the present specification as filed at p. 2, lines 18–20: "Rotigotine is only feebly soluble in hydrophobic polymers such as silicon[e], for example. For these reasons, in WO 99/49852 the adding of additives to improve the solution characteristics of the rotigotine is recommended. This is a matter of in particular hydrophilic polymers such as polyvinyl pyrrolidone (PVP)…" Even if, *arguendo,* Farinas does not "teach away" from use of solubilizers and/or crystallization inhibitors, Farinas, Lauterbach, and WO 99/49852 provide motivation toward using solubility-enhancers, such as PVP in the matrix. Applicant selected the opposite – a matrix free of solubilizers, crystallization inhibitors, and dispersants. So again, why would one of ordinary skill in the art be motivated from Farinas or Lauterbach to select a matrix free of solubilizers, crystallization inhibitors, and dispersants?

Applicant submits that the enormous selection process to select rotigotine, followed with at least 8 complex selections to make the claimed matrix after that, is at most an invitation to "try" or "experiment" with a large number of variables without any guidance from the cited art. This is not enough to establish a presumption of *prima facie* obviousness.

3. It Was Unpredictable That Rotigotine Would Work In a Matrix Free Of Solubilizer, Crystallization inhibitor and Dispersant

The Examiner in the Office Action bridging p. 9-p. 10 asserts that "one would have been motivated to try a dopaminergic agonist with the elimination of solvent, crystallization inhibitor, and dispersant with a reasonable expectation of success since Farinas suggests it within a finite number of identified possibilities."

First, as stated above, Farinas does not disclose a finite number of possibilities, *i.e.* one would have to mine through the at least six large compound categories set forth in Farinas, settle on dopamine agonists or antagonists, select dopamine agonists, test those, and then eventually settle on rotigotine. This is not an example of a finite number of possibilities contemplated by the Court in *KSR v. Teleflex.*

Second, since Lauterbach specifically mentions rotigotine and use of a solubility-enhancer, such as PVP, one of ordinary skill in the art would have expected to need a solubilizer, crystallization inhibitor, and/or dispersant for success. It is well known that the

performance of active agents obviously depends significantly on the character of the active agent, formulation conditions and manufacturing conditions. Thus, Applicant unexpectedly obtained success with a rotigotine base matrix free of a solubilizer, crystallization inhibitor, and dispersant.

4. It Was Unpredictable that a Rotigotine-Matrix Would Stay Storage Stable For 6 Months

On p. 10 of the Office Action, the "examiner notes that applicant is not claiming a storage-stable matrix and has failed to provide any objective evidence that compares the instant invention's stability to the closest prior art."

First, as amended herein, Claims 12 and 13 recite a matrix that is storage-stable for at least 6 months. Accordingly, even if *arguendo* one of ordinary skill would somehow have been motivated to (1) remove the solubilizer, crystallization inhibitor, and/or dispersant taught in the art, including Lauterbach, WO 99/49852, and Farinas and (2) prepare a matrix comprising rotigotine free base amorphous particles with a maximum mean diameter of 30 µm, it could not have been predicted that after 6 months storage, there would be no sign of the amorphous rotigotine particles recrystallizing or changing in particle size.

Second, Applicant's specification in at least Figure 4 shows the comparison of *in vitro* rotigotine flow rates that are achieved after applying on human skin a system according to Applicant's invention after 5 months storage (Charge 20204071) and a system described in WO 99/49852 (Charge WE116852). One of ordinary skill in the art understands that solubilizers, crystallization inhibitors and dispersants facilitate dissolution of the drug. "The active substance charge is limited by the solubility of the rotigotine in the respective solvent system." *See* specification as filed at p. 2, lines 2-3. "Rotigotine is only feebly soluble in hydrophobic polymers such as silicon[e], for example. For these reasons, in WO 99/49852 the adding of additives to improve the solution characteristics of the rotigotine is recommended. This is a matter of in particular hydrophilic polymers such as polyvinyl pyrrolidone (PVP)…" *See* specification as filed at p. 2, lines 18–20. One of ordinary skill in the art would expect that a matrix free of a solubilizer, crystallization inhibitor and dispersant would recrystallize and thus, not be storage-stable for 6 months. Figure 4 in Applicant's specification shows that "after five months storage at room temperature, the release behavior

of the TTS according to the invention remained unchanged (Fig. 4)." *See* specification as filed at p. 5, lines 10-12. But "[e]ven after six months storage at room temperature, the amorphous rotigotine particles in the silicon matrix showed no tendency to recrystalize." *See* specification as filed at p. 5, lines 1-5.

Therefore, Applicant maintains that with respect to Claim 12, it could not have been predicted by one of ordinary skill in the art at the time of the present invention that a storage-stable matrix could be prepared containing rotigotine base above its limit of solubility in the matrix polymer, yet without solubilizers, crystallization inhibitors or dispersants. With respect to Claim 13, it could not have been predicted by one of ordinary skill in the art at the time of the present invention that a storage-stable matrix could be prepared containing rotigotine base above its limit of solubility in the matrix polymer, yet without any excipient ingredient other than the matrix polymer and, optionally, one or more antioxidants

5. General Remarks

Applicant submits that a presumption of *prima facie* obviousness has not been established for Claims 12 and 13, for at least the following reasons:

- Farinas does not provide any pattern of preference for selecting rotigotine, much less rotigotine base;
- None of the cited documents teach or suggest a matrix free of solubilizer, crystallization inhibitor, and dispersant;
- No reasonable expectation of success existed that a TTS containing a matrix polymer wherein rotigotine is partly dissolved and partly present as amorphous particles having a maximum mean diameter of 30 μm, and wherein the matrix is free of solubilizer, crystallization inhibitor and dispersant, would work; and
- No expectation of success can reasonably be postulated as to achieving a storage-stable polymer matrix containing amorphous particles of rotigotine free base.

Each of Claims 14–19 and 29-31 depend directly or ultimately from Claim 12 or 13 and incorporates all limitations of Claim 12 or 13, and is therefore nonobvious for at least the same reasons that Claims 12 and 13 are nonobvious. Furthermore, on p. 7 of the Office Action, the Examiner asserts that "a flow rate of rotigotine through human skin that is therapeutically effective, upon application of the system at intervals of 1 to 7 days, would be an obvious expected property." This is an improper conclusion, as flow rate is controlled by numerous system factors. Since Applicant's matrix is free of a solubilizer, crystallization

inhibitor and dispersant and as discussed above, such matrix is not taught, disclosed or suggested in the cited art, the flow rate of rotigotine in Applicant's matrix is not an "obvious expected property."

Withdrawal of the present rejection under 35 U.S.C. § 103 is respectfully requested.

Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that all presently outstanding rejections be re-considered and withdrawn. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

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Attachments:
Declaration of Keith Ormand;
Exhibit A to the Declaration of Keith Ormand;
Replacement Sheet for Figure 1.